REMARKS

Claims 1-4, 6-10, 28-30 and 32 are pending in the application. Claims 1, 6 and 32 have been amended to expedite examination of the application, without prejudice to filing one or more divisional applications directed to the canceled subject matter thereof. Claims 5, 31 and 33-81 have been canceled without prejudice to filing one or more divisional applications directed to the subject matter thereof. Claims 11-27, 36-39, 41, 44-46, 51, 54, 56, 59, 61, 64, 66, 69, 72, 75, 78 and 81 have been withdrawn from consideration by the Examiner as being non-elected. No new matter has been added to the application by any of the foregoing amendments.

At pages 2-3 of the Office Action, the Examiner has requested confirmation of the provisional election of species of simvastatin as third component for initial examination in this application. Applicants respectfully confirm this election with traverse on the grounds that it would not constitute an undue burden on the examiner to search the other claimed third components.

At pages 3-5 of the Office Action, claims 1-10, 28-35, 40, 42, 43, 47, 48, 50, 52, 53, 55, 57, 58, 60, 62, 63, 65, 67, 68, 70, 71, 73, 74, 76, 77, 79 and 80 have been rejected under 35 U.S.C. §103(a) as obvious over U.S. Patent No. 5,846,966 ("Rosenblum et al.") in view of U.S Patent No. 5,698,527 ("Kim") and WO 2000/38725 ("Keller et al.").

For brevity, the reasons for rejection are not repeated herein but reference is made to the outstanding Office Action.

Applicants respectfully traverse this rejection and request that the rejection be reconsidered and withdrawn.

It is respectfully submitted that the combination of the references cited as rendering the claimed invention obvious is improper because there is no suggestion in the cited references to combine the claimed components of ezetimibe and nicotinic acid.

When making a rejection under 35 U.S.C. § 103, the Examiner has the burden of establishing a prima facie case of obviousness. In re Fritch, 23 U.S.P.Q.2d 1780, 1783 (Fed. Cir. 1992). The Examiner can satisfy this burden

only by showing an objective teaching in the prior art, or knowledge generally available to one of ordinary skill in the art, which would lead an individual to combine the relevant teachings of the references [and/or the knowledge] in the manner suggested by the Examiner. Id.; In re Fine, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988).

The mere fact that the prior art could be modified does not make the modification obvious unless the prior art suggests the desirability of the modification. In re Fritch, 23 U.S.P.Q.2d at 1784; In re Laskowski, 10 U.S.P.Q.2d 1397, 1398 (Fed. Cir. 1989); In re Gordon, 221 U.S.P.Q. 1125, 1127 (Fed. Cir. 1984).

"It is impermissible to use the claimed invention as an instruction manual or 'template' to piece together the teachings of the prior art so that the claimed invention is rendered obvious....'[o]ne cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention.'" In re Fritch, 23 U.S.P.Q.2d at 1784 (quoting In re Fine, 5 U.S.P.Q.2d at 1600).

"The ultimate determination of patentability must be based on consideration of the entire record, by a preponderance of evidence, with due consideration to the persuasiveness of any arguments and any secondary evidence." Manual of Patent Examining Procedure, (Rev. 1, Feb. 2003) § 716.01(d) and In re Oetiker, 24 U.S.P.Q.2d 1443, 1444 (Fed. Cir. 1992).

Rosenblum et al. do not suggest or disclose the combination of ezetimibe and nicotinic acid. Kim discloses steroidal glycoside cholesterol absorption inhibitors that can be administered in combination with niacin. Keller et al. disclose combinations of an ileal bile acid transport inhibitor or CETP inhibitor and a cholesterol absorption inhibitor such as ezetimibe, but not the combination of ezetimibe and nicotinic acid.

None of the foregoing references, combined as set forth in the Office Action, would motivate one of ordinary skill in the art to combine a substituted azetidinone cholesterol absorption inhibitor, such as ezetimibe, with nicotinic acid. Ezetimibe is not a steroidal glycoside.

The steroidal glycosides disclosed by Kim are structurally very dissimilar to the presently claimed substituted azetidinone compound ezetimibe. Given their large molecular size, it is unlikely that Kim's steroidal glycosides are absorbed through the intestine. In contrast, multiple peaks in plasma concentration-time profiles suggest that the glucuronide conjugate of ezetimibe undergoes enterohepatic recycling before elimination. See ZETIA™ (ezetimibe) Tablets Package Insert at column 2 (Merck/Schering-Plough Pharmaceuticals) (October 2002), included in the Information Disclosure Statement filed concurrently herewith. This enterohepatic recycling can enhance efficacy.

Kim's steroidal glycoside compounds have not been commercialized by Merck & Co., Inc. (the assignee of the Kim patent). Rather, Merck is the joint venture partner of Schering-Plough (assignee of the present application) in marketing the cholesterol absorption inhibitor ZETIA™ ezetimibe formulation. ZETIA was launched in late 2002 and global sales of ZETIA in the 2003 fourth quarter totaled $165 million, with U.S. sales of $144 million. Press Release: Schering-Plough Reports Financial Results for 2003 Fourth Quarter, Full Year Monday January 26, 6:33 am ET.

No data is presented in the Kim reference to support efficacy of a combination of steroidal glycoside and niacin. One skilled in the art would not be motivated to combine ezetimibe and nicotinic acid based upon the disclosure of Kim since the steroidal glycoside and ezetimibe molecules are so structurally dissimilar.

As shown in Table 1 of the present application, Compound XII (a substituted azetidinone cholesterol absorption inhibitor) reduced plasma cholesterol levels and the accumulation of hepatic cholesteryl esters in the cholesterol-fed hamsters. Niacin reduced plasma triglyceride levels, but did not significantly reduce the cholesterol levels. The combination of Compound XII and niacin resulted in reductions in plasma and hepatic cholesterol levels, as well as plasma triglycerides (Table 1). These results indicate that the combination of the cholesterol absorption inhibitor of Compound XII and niacin can have additive

effects on treating hyperlipidemia in male Golden Syrian hamsters, by reducing both cholesterol and triglyceride levels.

Neither Rosenblum et al, Kim, nor Keller et al., taken alone or combined as set forth in the Office Action, provides motivation for combining ezetimibe and niacin. Accordingly, reconsideration and withdrawal of the §103(a) rejection is respectfully requested.

Applicants respectfully request that the Examiner return an initialed PTO-1449 form for the Information Disclosure Statement submitted herewith and each of the Information Disclosure Statements submitted on October 28, 2003 and January 8, 2004,indicating that the Examiner has considered each of the references cited therein.

In view of the foregoing remarks, it is respectfully submitted that all of the pending claims in the present application are distinguishable from the cited prior art. Accordingly, reconsideration and withdrawal of the rejection and an early Notice of Allowance are respectfully requested.

Respectfully submitted,

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Date: February 12, 2004

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